Remarks

Reconsideration of this Application is respectfully requested.

Claims 166, 168, 170, 177 and 247 are pending in the application, with claim 166 being the independent claim.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 102(e)

Claims 170 and 247 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Chien *et al.* (U.S. Pat. No. 6,150,087). Applicants respectfully traverse the rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); *see also* MPEP § 2131. Chien discloses a peptide sequence 50 amino acids in length (AA1850-AA1900) which *comprises* the sequence GVAGALVAFK. (*See* Chien, col. 27, second paragraph). Applicants respectfully disagree with the Examiner's contention that since the claims contain the phrases "conjugate is" and "epitope is linked" the language is considered open, and therefore can encompass the peptide attached to other amino acids and further to tetanus toxoid. (Office Action, pages 2-3). Closer examination of claim 170 shows that the CTL epitope of the CTL/HTL conjugate *is* the isolated peptide of claim 166. Claim 166 is directed to a group isolated peptides containing the elected peptide. Therefore, contrary to the assertion of the Examiner, the CTL epitope cannot contain

additional amino acids because it is limited to the isolated peptides recited in claim 166. Since none of the peptides disclosed in Chien correspond exactly to Applicants' claimed peptide, Chien fails to teach every aspect of the claimed invention. Accordingly, Applicants respectfully assert that claims 170 and 247 are not anticipated by Chien and request that the rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103

Claims 166, 168, 170, 177 and 247 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Chien, in view of Berzofsky *et al.* (U.S. Pat. No. 5,980,899) and Guo *et al.* (*Nature 360*:364-366 (1992)). Applicants respectfully traverse the rejection for the reasons of record and those listed below.

I. The Examiner has improperly relied upon an inherency argument.

As stated previously, Applicants assert that the Examiner has improperly relied on the unexpected properties of the claimed peptide *identified by the Applicants* in the obviousness analysis. Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). The Examiner extends this improper analysis by arguing that "the functional attributes of claim 166 would presumably be present in the peptide of Chien et al. in that said larger peptide would be processed in vivo to yield the peptide of claim 166." (Office Action, page 6.) The Examiner, however, has not provided any evidence to support this assertion, nor does the Examiner show that Chien has any teaching of the unexpected properties previously presented in Applicants' Amendment and Reply dated August 29, 2005. (*See* for

example, page 11 of the Applicants' Reply describing the strong CTL-inducing response of the Applicants' peptide.) Instead, the Examiner provides the same recitation from the M.P.E.P. § 2145 regarding recognition of additional advantages or latent properties present in the prior art and reiterates the same five sentences in support of his stance rather than substantively address the previous arguments made by Applicants.

Even assuming that the larger peptide of Chien would be processed *in vivo* to produce Applicants' claimed peptide (which it would not necessarily do as described further below), the Examiner is improperly relying on the finding of unexpected functional attributes of the claimed peptide *identified by the Applicants* to use Chien in combination with Berzofsky and Guo, in an obviousness rejection.

Applicants have cited Yewdell, Eisenlohr and DelVal (Amendment and Reply of November 15, 2005, and Amendment and Reply dated August 29, 2005) in support of the proposition that it is difficult to identify exactly which specific peptides are capable of inducing an immune response within a given longer sequence. In the most recent Office Action, the Examiner dismisses Yewdell because it was published after the filing date of the claimed invention. However, Yewdell discloses the reasoning for why it is, and has been difficult to predict immunogenic peptides, and provides the theory of immunodominance. Immunodominance has been occurring in nature long before its recognition in Yewdell; therefore, the publication date of Yewdell in relation to the inability to pick immunogenic peptides is irrelevant. Furthermore, as stated previously, the Examiner insists on relying on the unexpected functional attributes of the claimed peptide *identified by the Applicants* to support the obviousness argument. As noted above, however, it is improper to do so as obviousness cannot be predicated on what is

not known at the time an invention is made. As described above, the unexpected functional attributes of Applicants' claimed peptide was not known or described by Chien, Berzofsky and/or Guo.

The Examiner again also states that Eisenlohr "teaches that flanking sequences can also positively effect the presentation of an immunogenic peptide." (Office Action, page 8.) Applicants emphasize, however, that while flanking resides *may* be able to positively affect the presentation of an immunogenic peptide, Eisenlohr also teaches that the addition of flanking residues can also destroy the antigenicity of a particular peptide. *See* Eishelohr, page 485, first paragraph. Therefore, an epitope embedded within a larger sequence may be processed differently, and thus have different immunogenicity than the same epitope free of flanking or surrounding amino acid residues. In view of Eisenlohr, the Examiner cannot simply assume that the longer, 50 amino acid peptide in Chien will be processed *in vivo* to generate Applicants' claimed peptide. Again, even assuming that the longer peptide would be processed *in vivo* to produce Applicants' claimed peptide, the Examiner cannot rely on the unexpected property identified by the Applicants, in the obviousness analysis.

Thus, as discussed above, the Examiner's obviousness analysis cannot rely on the unexpected property of the claimed peptide identified by the Applicants. As discussed below, Applicants assert that, when the proper criteria in an obviousness analysis are considered, that the Examiner has not established a *prima facie* case of obviousness.

II. The Examiner has not established a prima facie case of obviousness.

As described above, in an obviousness analysis, it is improper to rely on the inherency of a certain feature to provide a reason or motivation to combine the cited

references. In order to establish a *prima facie* case of obviousness, the proper analysis is to first consider whether the following three criteria are met: (1) there must be some reason, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2143. "[I]n formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Memorandum from the United Patent and Trademark Office, "Supreme Court decision on *KSR Int'l. Co. v. Teleflex Inc.*," (May 3, 2007) at page 2.

Applicants again assert that the Examiner has not provided an adequate reason to combine the reference teachings and arrive at Applicants' claimed invention, and thus the first criteria necessary to establish a *prima facie* case of obviousness has not been met.

Applicants again note that currently pending claims 166, 168, 170, 177 and 247 are directed to an isolated peptide selected from a group which includes Applicants' elected peptide GVAGALVAFK. Chien, as discussed above, does not dislcose every element of Applicants' claimed invention. This is supported by the Examiner's own statement that "Chien et al. do not teach the peptide of claim 166/168." (Office Action mailed November 15, 2005, page 4.)

The Examiner has alleged that Chien, in view of Berzofsky, renders the claims obvious. As noted previously, the Berzofsky article focuses on the NS5 region; the only exemplification in Berzofsky is with regard to the identification of a particular peptide

within the NS5 region. *See* Berzofsky, Examples 1-4. The preferred peptides of Berzofsky, as listed in Fig. 1A, all correspond to peptides of the NS5 region. Berzofsky, Fig. 1A.

While Berzofsky generally describes other regions of HCV, it does not provide any guidance with regard to which specific regions of the HCV genome necessarily contain good targets for CTL, nor does it contain any guidance to identify Applicants' claimed peptide. A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *See* M.P.E.P. § 2141.02(VI) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)); *see also Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1093-94 (Fed. Cir. 1985) ("The well established rule of law is that each prior art reference must be evaluated as an entirety . . . ."). That is, "[t]here is no suggestion to combine . . . if a reference teaches away from its combination with another source." *Tec Air, Inc. v. Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999); *see also KSR* at 12 (reaffirming "the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious") (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)).

Applicants' elected peptide, GVAGALVAFK, is neither discussed, nor described in Berzofsky. In addition, the peptides of Applicants' claimed invention are determined using techniques which do not rely on the amphipathicity algorithm of Berzofsky. Berzofsky does not disclose the techniques Applicants' utilized to identify candidate CTL epitopes. Therefore, at best, Berzofsky is an invitation to identify a peptide in the NS5 region. Given the relatively large number of possible epitopes that could be identified

within the HCV genome, the Berzofsky article, without more, cannot be viewed to provide a sufficient reason to modify the art to arrive at Applicants' claimed invention. As such, Chien in view of Berzofsky does not render the claims obvious.

The Examiner has also alleged that Chien, in view of Berzofsky, and further in view of Guo allegedly renders the claims obvious. Guo generally describes how CTL recognize viral peptides complexed with MHC and that these peptides generally are 9 to 11 amino acids in length. Guo, page 364. While Guo discloses peptide sequences from several proteins including ribosomal 60S, human Hsp70, and influenza NP (Guo, Table 1), Guo does not contain any discussion regarding the identification of CTL epitopes within the HCV genome, nor does Guo disclose Applicants' elected peptide.

Accordingly, Chien, in view of Berzofsky, and further in view of Guo provide no reason to combine or modify the references, nor do they teach or suggest all of the claim limitations. At best, Berzofsky and/or Guo provide an invitation to experiment.

Thus, Applicants assert that the criteria requiring that a reason, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify Chien or to combine reference teachings, has not been met. Therefore, a *prima facie* case of obviousness, with respect to claims 166, 168, 170, 177 and 247 has not been established. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

III. Even assuming that a prima facie case of obviousness has been established, Applicants assert that this prima facie case of obviousness has been rebutted.

Assuming, *arguendo*, that the Examiner has established a *prima facie* case of obviousness, Applicants assert that the *prima facie* case of obviousness has been

rebutted. Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. MPEP § 716.02; *see In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987). Applicants emphasize that the unexpected property of Applicants' claimed peptide is sufficient to rebut a *prima facie* case of obviousness. As discussed in detail above, the unexpected property of Applicants' claimed peptide cannot be the reason relied upon by the Examiner to establish the *prima facie* case of obviousness itself.

As discussed previously in the Amendment and Reply filed November 29, 2004 and again in the Amendment and Reply filed on December 15, 2006, Table XXIII ("Immunogenicity of identified supermotif-bearing peptides") shows that Applicants' elected peptide GVAGALVAFK exhibits the strongest CTL-inducing response in transgenic mice as compared to any of the other peptides listed in Table XXIII and compared to any of the other peptides which share the same A3 motif. Applicants also point out that in Table XVI, Applicants' elected peptide GVAGALVAFK exhibits one of the strongest binding affinities as compared to over 400 other peptides which share the same A3 motif.

Thus, the CTL-inducing and binding characteristics of the GVAGALVAFK peptide, as determined by Applicants, demonstrate that the GVAGALVAFK peptide indeed has unexpected properties. In view of the improved binding properties of the GVAGALVAFK peptide as compared to over 400 other peptides sharing the same motif, and in view of the significantly greater CTL induction generated as compared to other peptides sharing the same motif, Applicants assert that this evidence of unobvious or unexpected advantageous properties is present and is sufficient to rebut the alleged

prima facie case of obviousness. It is the functional characteristic of the peptide, as determined by the Applicants, which renders the peptide to have an unexpected property, and thus renders the peptide non-obvious in view of the prior art. A showing of nonobviousness does not require that these features necessarily need to be present as limitations of the claims.

Based on the above, Applicants assert that even assuming a *prima facie* case of obviousness has been established, a *prima facie* case of obviousness has been rebutted using the evidence described above.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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